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## A CASE OF QUADRUPLE CANCER INCLUDING URINARY BLADDER, ORAL CAVITY, STOMACH AND LUNG

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A 67-year-old man, who had smoked heavily for many years, was found in 1997 to have bladder tumors, and transurethral resection of the bladder tumor (TUR-Bt) was performed. Histopathological diagnosis was urothelial carcinoma (G2>G3, pTa, N0, M0, ly0, v0). In December, 1998, he noticed an oral cavity tumor. After preoperative radiation therapy (total 40 Gy, 17 times), surgical treatment was undertaken. Histopathological diagnosis was well differentiated squamous cell carcinoma (pT2, pN2b, M0). In February, 2000, gastric tumor was detected by endoscopic examination, and subtotal gastrectomy and Roux en Y operation were performed. Histopathological diagnosis was well differentiated adenocarcinoma (pT2, pN0, M0, P0, CY0). A chest computed tomographic (CT) scan revealed a solitary lung tumor in April, 2000. Partial pneumonectomy was performed, and histopathological diagnosis was poorly differentiated adenocarcinoma (pT1, N0, M0, P0). In April, 2000, multiple lesions of bladder cancer in the neck of the urinary bladder and posterior urethra were found and radical cystoprostatourethrectomy combined with lymph node dissection and bilateral cutaneous ureterostomy were performed (urothelial carcinoma, G3, pT4a, pN2, M0, pL2, pV0, pR0). Since then, the patient has been followed carefully.

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**Key words:** Quadruple cancer, Urinary bladder, Oral cavity, Stomach, Lung

### INTRODUCTION

As many reports on the incidence of multiple primary cancers have been published since Billroth's first description in 1889<sup>1)</sup> and with advanced diagnostic procedures and improved survival techniques, detection of multiple cancers is no longer so uncommon. Nevertheless, quadruple treated primary cancers remain rare, and we found no report of a patient with the combination of bladder, oral cavity, gastric and lung cancers.

We report this rare case here with some discussion of relevant literature.

### CASE REPORT

A 67-year-old Japanese man visited our hospital with a complaint of macroscopic hematuria in July 1997. The patient had a previous history of colon polyp treated by endoscopic resection and verified adenoma. He had smoked 20 cigarettes a day for 45 years and has no family history of cancer. Physical examination revealed no palpable mass and no swollen lymph nodes. A routine blood analysis did not reveal any abnormalities and the serum tumor markers were all within the normal range. He was admitted to hospital and underwent further

examinations. Neither drip infusion pyelography (DIP) nor abdominal ultrasonography provided any abnormal findings and only a pelvic computerized tomography (CT) scan revealed thickness in a part of the urinary bladder. However, malignant cells (class V) were pointed out in his urine. Cystoscopic examination was performed, showing two small papillary bladder tumors. Transurethral resection of the bladder tumors (TUR-Bt) and random biopsy of bladder mucosa were performed in November 1997. Histopathological examinations revealed that the tumors were urothelial carcinoma (G2>G3, pTa, N0, M0, ly0, v0), and some parts of random biopsies showed dysplasia. The patient received intravesical instillation treatment with pirarubicin hydrochloride for adjuvant therapy once a week, for a total of 8 times and has been followed closely since then.

In December 1998, he noticed a nodular lesion in the oral cavity, later diagnosed as tongue cancer. After preoperative radiation therapy (total 40 Gy, 17 times), he received surgical resection of this lesion and swelling lymph nodes in February, 1999, at Osaka Center Hospital for Adult Diseases. Histopathological diagnosis was well differentiated squamous cell carcinoma (pT2, pN2b, M0) (Fig. 1).

In a routine check of the upper digestive tract by endoscopic examination, gastric tumor (Borrmann III type) was detected in February, 2000. Subtotal gastrectomy, lymph node dissection and Roux en Y operation were performed in April, 2000, and

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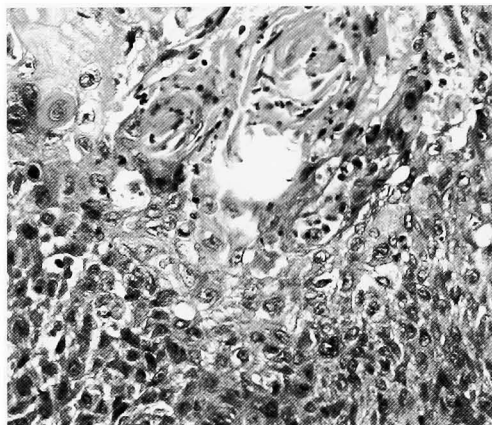


Fig. 1. Histopathology of oral cavity cancer: well differentiated squamous cell carcinoma (HE,  $\times 400$ ).

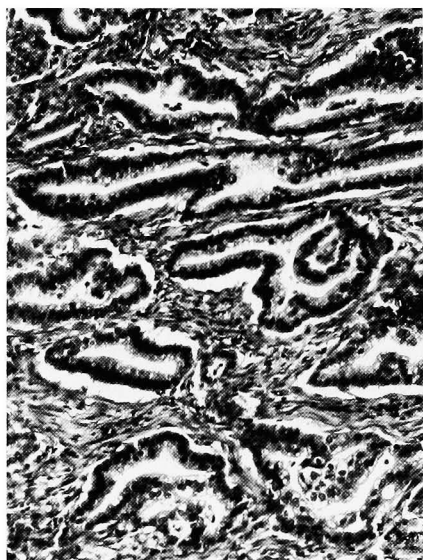


Fig. 2. Histopathology of gastric cancer: well differentiated adenocarcinoma (HE,  $\times 200$ ).

histopathological diagnosis was well differentiated adenocarcinoma (pT2, pN0, M0, P0, CY0) (Fig. 2).

Postoperative evaluation of the gastric cancer using chest computerized tomography (CT) scan revealed a solitary mass in the left upper lobe of the lung (S1+2, 1.6 cm in diameter, Fig. 3) in April, 2000. Partial pneumonectomy was performed in December, 2000, and histopathological diagnosis was poorly differentiated adenocarcinoma (pT1, N0, M0, P0, Br-).

Unfortunately, in April, 2000, cystoscopy revealed multiple lesions of bladder cancer in the neck of the urinary bladder and posterior urethra. After surgical treatments of the gastric and lung cancers at Osaka Center Hospital for Adult Diseases, radical cystoprostatectomy combined with lymph node dissection and bilateral cutaneous ureterostomy was performed in November, 2000. Histopathological examination showed tumor invasion into prostate and metastases in two right iliac lymph

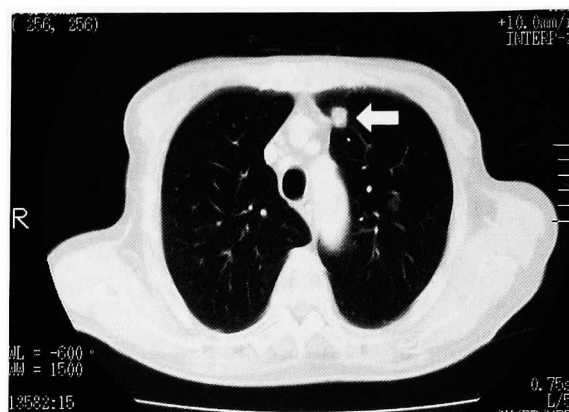


Fig. 3. Chest CT revealed a solitary mass in the left upper lobe of the lung (S1+2, 1.6 cm in diameter).



Fig. 4. Histopathology of recurrence lesions of bladder cancer: urothelial carcinoma (HE,  $\times 400$ ).

nodes (urothelial carcinoma, G3, pT4a, pN2, M0, pL2, pV0, pR0) (Fig. 4). Since then, the patient has been followed carefully in our hospital.

## DISCUSSION

In 1932, Warren and Gates<sup>2)</sup> proposed the first criteria for multiple malignant tumors, which stated that: 1) Each of the tumors must present a definite picture of malignancy, 2) each must be distinct, and 3) the possibility that one is a metastasis of the other must be excluded.

In 1961, Werthamer et al.<sup>3)</sup> proposed more restrictive criteria, stating that: 1) The malignancies must be primary in different organs, 2) paired-organ primary malignant degenerations, whether synchronous or metachronous, should be considered as representing one tumor, 3) multiple malignancies in the same organ should be considered as representing a single primary malignancy, 4) the lower intestinal tract, as well as the uterus, should be considered a

single organ, 5) there must be histologic evidence of aberrant growth in the organ tissue and 6) a careful histologic attempt to exclude metastasis should be made.

The patient described in this report had four separate malignancies: urothelial carcinoma in the urinary bladder; well differentiated squamous cell carcinoma in the oral cavity; well differentiated adenocarcinoma in the stomach; and poorly differentiated adenocarcinoma in the lung. Both the gastric cancer and lung cancer were pathologically categorized as the same adenocarcinoma; however, their pathological stages were pT2 and pT1, without any invasion into lymphatic nor vascular vessels. This suggests these malignancies are two different primary cancers and Werthamer's criteria of quadruple cancer were filled.

For classification of synchronous or metachronous tumor based on the development interval, Moertel et al.<sup>1)</sup> employed 6 months and Kitabatake et al.<sup>4)</sup> employed 1 year. In our patient, the interval between the first (urinary bladder) and second (oral cavity) tumors was 17 months, corresponding to metachronous tumors, and to the third (stomach) and fourth (lung) tumors another 16 months, corresponding to synchronous lesions.

Multiple malignant neoplasms do not occur infrequently, but a quadruple cancer remains rare; the incidence of this type of cancer is 0.00029–0.00675%<sup>2)</sup>, including autopsy cases. Clinically, quadruple cancer is very rare, and our case is only the fifteenth case reported. Additionally, we could find only one case report about quintuple cancer<sup>5)</sup>

Some authors have proposed that immunologic impairment, genetic factors, and repeated exposure to a specific carcinogen (smoking, radiation, chemotherapy etc.) may be a cause of multiple primary neoplasms<sup>6)</sup> Murata et al. reported a case of quadruple cancer including Bowen's disease after arsenic injections for the treatment of syphilis<sup>7)</sup>

Recent advances in genetic studies have revealed an association between multiple primary cancer and abnormalities of the p53 tumor suppressor gene or infrequent frameshift mutations<sup>8,9)</sup>.

We did not investigate the molecular biological features of the tumors in our patient and the exact cause of quadruple cancer is unknown, but his past heavy smoking may have contributed to the malignancies<sup>10)</sup>

Multiple cancers are usually found in advanced clinical stages and it is different to resect such tumors by surgery<sup>11)</sup> These findings indicate that preoperative diagnosis of multiple synchronous cancers is difficult to achieve in their asymptomatic or early phase. In our case, the oral cavity tumor was found during the postoperative follow-up period for bladder cancer, and the clues for the diagnosis of gastric and

lung cancer, which were asymptomatic, were obtained in routine postoperative evaluations. This case suggests that the possible existence of unknown second or third cancers should be kept in mind when making a postoperative evaluation of malignant disease is made, although the risk is likely to be very low.

Multiple cancers might be diagnosed, when one of these tumor shows more accelerated growth than the other cancers and, thereafter, becomes symptomatic. In such situations, the diagnosis of synchronous cancers might be established too late to achieve successful treatment. However, metachronous multiple cancers might pose a different situation. As the patient might receive careful follow-up after treatment of a first cancer, subsequent cancers have a greater chance of being discovered and treated in their early clinical stages and the patient's prognosis might depend on the curability of the first cancer, as in this presented case.

Our patient needs strict monitoring of the whole body because of the risk for not only novel metastasis of bladder cancer and recurrences of other cancer lesions but also the development of a fifth cancer. He has a previous history of colon polyp, verified adenoma, and in hindsight thought to be a precancerous lesion<sup>12)</sup> Therefore there is also a risk of recurrence of colon polyp and colon carcinogenesis in the future.

In summary, this case is interesting because of the rare occurrence of quadruple cancer, including urinary bladder, oral cavity, stomach and lung cancers, in a patient with a history of long-term heavy smoking.

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## 和文抄録

## 膀胱癌，口腔底癌，胃癌，肺癌による異時性四重複癌の1例

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症例は長期にわたるヘビースモーカーの67歳，男性，1997年に膀胱に発生した尿路上皮癌に対し，大野記念病院において経尿道的膀胱腫瘍切除術を施行されている（G2>G3，pTa，N0，M0，ly0，v0）．1998年12月に大阪成人病センターにおいて口腔底に発生した高分化型扁平上皮癌に対して，放射線療法後（40 Gy，17回），外科的治療を受けた（pT2，pN2b，M0）．その際の全身検索において胃に高分化型腺癌を発見されたため，同院において胃亜全摘出術を施行されている（pT2，pN0，M0，P0，CY0）．さらに2004年4月にフォローの胸部CT検査において左肺上葉に孤在性の低分化型腺癌が発見され，肺部分切除術を施行された（pT1，N0，M0，P0，Br-）．以後，

経過を観察されていたが，2000年11月に膀胱から後部尿道にかけての尿路上皮癌の再発を認めたため，大野記念病院において根治的膀胱全摘術ならびに両側尿管皮膚瘻作成術を施行している（pT4a，pN2，M0，pL2，pV0，pR0）．医学の発展に伴い，近年においては，重複癌が発見されることは決して珍しいことではなくなりつつあるが，なお自験例の様に，四つの異なった臓器にそれぞれ由来の異なる悪性腫瘍の発生を認める症例は非常に稀であり，今回文献的考察を加えて報告した．重複癌の背景には何らかの発癌要因の存在が考えられており，自験例においても今後とも，注意深いフォローが必要と考えられた．

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